REMARKS

Claims 23-38 were pending in the present application. Applicant has cancelled claims 28-29 and 33, without prejudice, and have added new claims 39-42. Accordingly, claims 23-27, 30-32 and 34-42 will be pending upon entry of the instant amendment. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite prosecution of the application. Support for any claim amendment and new claims 39-42 can be found throughout the specification and claims as originally filed. Specifically, support may be found at page 3, beginning on line 11, at page 11, beginning on line 4, at page 14, beginning on line 23, at page 15, beginning on line 19, on page 16, beginning at line 3, at page 18, beginning on line 4 and at page 107, beginning on line 15. No new matter has been added by way of amendment. Applicant respectfully requests that the amendments and remarks made herein be entered and fully considered.

I. Rejection of Claims 28 and 29 Under 35 U.S.C. § 101

Claims 28 and 29 are rejected under 35 U.S.C. § 101 because they encompass products of nature. Applicant has canceled claims 28 and 29, thereby obviating the rejection.

II. Rejection of Claims 23-25 Under 35 U.S.C. § 112, second paragraph

Claims 23-25 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner describes claims 23-25 as confusing because, among other things, "one cannot tell from a polypeptide what the structure is for noncoding sequences which may flank the coding sequence."

In an effort to expedite prosecution, and without in any way acquiescing to the Examiner's rejection, Applicant has amended claims 23-25 and 30-31 to specify that the claimed polypeptide is encoded by either i) SEQ ID NO:19 (the open reading frame of the claimed polypeptide) rather than by SEQ ID NO:17 (the full length nucleic acid sequence including non-coding regions); or ii) the coding region of the cDNA deposited with the ATCC. By way of amendment Applicant has clarified that the claimed polypeptide is encoded by *the coding* portion of the sHVEM2 sequence. Claims 23-25 and 30-31 as amended describe proteins which are encoded by nucleotide sequences having a certain degree of sequence identity to the sHVEM

open reading frame (SEQ ID NO:19). Support for the claim amendment can be found in the specification, for example, on page 16, line 3. Applicant therefore respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §112, second paragraph rejection.

III. Rejection of Claims 32-34, 37, and 38 Under 35 U.S.C. § 112, second paragraph

Claims 32-34, 37 and 38 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserts that "The specification speculates upon possible biological activities for a TANGO-69 receptor, but does not teach all of the possible activities for the receptor." The Examiner then concludes that "[i]t is not clear what is encompassed with a "human TANGO-69 receptor activity", and therefore unclear what polypeptides are encompassed by the claim."

Applicant respectfully traverses the rejection, however in the interest of expediting prosecution, and in no way acquiescing to the Examiner's rejection, Applicant has amended claims 30 and 32 to replace the term "TANGO-69 receptor activity" with the following: "wherein the polypeptide has an activity selected from the group consisting of: (i) the ability to bind a TANGO-69-receptor ligand; and (ii) the ability to modulate the interaction of a TANGO-69-receptor ligand with mHVEM." This claim amendment obviates the indefiniteness of the rejected claims by further defining the TANGO-69 receptor activities. Support for this claim amendment can be found, for example, on pages 11, 18 and 107 of the specification. Applicant therefore respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §112, second paragraph rejection.

IV. Rejection of Claims 27, 29, 33 and 34 Under 35 U.S.C. § 112, second paragraph

Claims 27, 29, 33 and 34 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims were rejected since they are dependent claims which recite "further comprising an amino acid sequence which is [a larger %] identical..."

In an effort to expedite prosecution, and without in any way acquiescing to the Examiner's rejection, Applicant has amended claims 27 and 34, as suggested by the Examiner, to read "wherein the amino acid is" rather than "further comprising an amino acid". Applicant has

additionally canceled claims 29 and 33. Therefore, in light of these claim amendments and claim cancellations, Applicant respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §112, second paragraph rejection.

V. Rejection of Claims 28, 29, 30-34, 37 and 38 Under 35 U.S.C. § 112, first paragraph (Written Description)

Claims 28, 29, 30-34, 37 and 38 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was divided into two aspects, one involving "naturally occurring allelic variants" over claims 28 and 29, and one involving "a human TANGO-69 receptor activity" over claims 30-34, 37 and 38.

Claims 28 and 29 were rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserts that "[t]he specification discloses only one allele within the scope of the genus: SEQ ID NO:18" and that "[t]here is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO:18 relates to the structure of different alleles." In an effort to expedite prosecution, and without in any way acquiescing to the Examiner's rejection, Applicant has canceled claims 28 and 29, thereby obviating the Examiner's rejection. Therefore, Applicant respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §112, first paragraph rejection.

Claims 30-34, 37 and 38 were rejected under 35 U.S.C. §112, first paragraph, as the Examiner asserts that "[t]he specification speculates upon possible biological activities for a TANGO-69 receptor, but does not teach all the possible activities of the receptor." The Examiner further states that "[t]he specification provides no guidance as to what regions of the protein structure are necessary for any of the protein's activities."

Applicant respectfully traverses the foregoing rejection, however in the interest of expediting prosecution, and in no way acquiescing to the Examiner's rejection, Applicant has amended claims 30-32 and 34 to replace the term "TANGO-69 receptor activity" with the following: "wherein the polypeptide has an activity selected from the group consisting of: (i) the ability to bind a TANGO-69-receptor ligand; and (ii) the ability to modulate the interaction of a TANGO-69-receptor ligand with mHVEM." Applicant has additionally amended a) claim 30 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 95%

identical to the nucleic acid sequence of SEQ ID NO:19; b) claim 31 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 98% identical to the nucleic acid sequence of SEQ ID NO:19; c) claim 32 to read that the polypeptide comprise an amino acid sequence which is at least 95% identical to the amino acid sequence of SEQ ID NO:18; and d) claim 34 to read that the polypeptide of claim 32 is at least 98% identical to the amino acid sequence of SEQ ID NO:18. Finally, Applicant has cancelled claim 33 without prejudice.

Therefore, the polypeptides described in remaining claims 30-32, 34, 37 and 38 now only vary by either 5% or 2% from SEQ ID NO:19 or 18 and the polypeptides described in these claims must additionally have activities specific to TANGO-69 receptor molecules as defined in the specification. The limitations within these amended claims are fully enabled within the specification as Applicant has provided teachings for every element needed for one of skill in the art to practice the claimed invention.

Contrary to the Examiner's assertion that "the specification provides no guidance as to what regions of the protein structure are necessary for any of the protein's activities", Applicant has taught that the molecules of the invention are members of the Tumor Necrosis Factor Receptor (TNFR) superfamily and that members of this superfamily characteristically have cysteine-rich subdomains in their extracellular, ligand binding domain. The specification then provides a detailed disclosure as to where these conserved cysteine-rich subdomains are located within each of the molecules of the invention (beginning on page 2 of the specification). As described on page 3 of the specification, the

> sHVEM2 protein possesses three of the four cysteine-rich repeats/domains characteristic of members of the TNFR family. The first cysteine rich domain is 34 amino acids long (amino acid 42 to about amino acid 75 of SEQ ID NO:18; SEQ ID NO:23). The second cysteine rich domain is 42 amino acids long (amino acid 78 to about amino acid 119 of SEQ ID NO:18; SEQ ID NO:24). The third cysteine rich domain is 42 amino acids long (amino acid 121 to about amino acid 162 of SEQ ID NO:18; SEQ ID NO:25).

These characteristic cysteine-rich domains play a role in the molecule's ability to bind ligands. Therefore, contrary to the Examiner's assertions, Applicant has taught the regions which are associated with the protein's activity. Moreover, as discussed below, Applicant has also taught how to alter regions of the polypeptide in order to generate other proteins of the invention. Firstly, by having taught which regions of the polypeptide are associated with the protein's activity, Applicant has taught which regions of the polypeptide are amenable to

alterations as well as those which are not amenable to alterations. Secondly, the specification additionally teaches one how to generate functional variants by performing conservative substitutions within the polypeptide used in the claimed invention. As defined on page 37, "[c]onservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." The Applicant has also defined which of the amino acids have similar side chains, thereby providing a skilled artisan the necessary tools to generate functional variants of the claimed polypeptide.

Finally, Applicant has provided teachings for one of skill in the art to be able to perform assays to determine whether or not specific sequences have the desired TANGO-69 activity. As taught on page 18 of the specification, TANGO-69-receptor activities include (1) the ability to form protein:protein interactions with proteins in the TANGO-69-receptor signalling pathway; and (2) the ability to bind a TANGO-69-receptor ligand, e.g., the ability to bind LIGHT/TANGO-69 or LTα. As taught on page 11 of the specification, TANGO-69 receptors have the ability to bind a mHVEM ligand and therefore have the ability to modulate the biological activities exerted by the mHVEM signaling pathway. Based on these activities, one can perform assays on specific sequences to determine whether or not such sequences have the desired biological activities. Such assays include, for example, assays which (1) monitor protein:protein interactions with proteins in the TANGO-69-receptor signalling pathway; and (2) monitor binding of a TANGO-69-receptor ligand, e.g., the ability to bind LIGHT/TANGO-69 or LTα or the ability to interfere with the binding of a TANGO-69-receptor ligand to mHVEM. In fact, example 3 on page 107 of the specification discloses a specific binding assay to determine whether the TANGO-69 receptor has the ability to block binding of TANGO-69 receptor ligands to mHVEM. Performing such assays to determine whether or not a variant of SEQ ID NO:18 has the desired properties would not constitute undue experimentation. Therefore, Applicant has provided all of the necessary information to enable one of skill in the art to 1) identify regions within the claimed polypeptide which may be altered while maintaining activity; 2) generate variants; and 3) perform assays to determine whether or not the sequences generated do in fact have the desired biological activity.

Therefore, Applicant submits that the specification provides sufficient disclosure to show that Applicant was in possession of the claimed invention at the time of filing and hence

Applicant respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §112, second paragraph rejection.

VI. Rejection of Claims 23, 24, 26-38 Under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 23, 24, 26-38 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for variants of SEQ ID NO:18 which are able to interfere with the ability of LIGHT/TANGO-69, LT. alpha., or HSV gD to bind to mHVEM, does not reasonably provide enablement for all variants, or variants with any "TANGO-69 receptor activity." The Examiner concludes that "Considering the limited teachings in the specification, and the unpredictability of biological activity for members of the TNFR superfamily, it is maintained that the specification is enabling only for variants which exhibit the disclosed biological activity of interfering with the ability of LIGHT/TANGO-69, LT. alpha., or HSV gD to bind mHVEM." Applicant respectfully traverses the foregoing rejection, however in the interest of expediting prosecution, and in no way acquiescing to the Examiner's rejection, Applicant has amended claims 23, 26, 27, 30, 31, 32 and 34 to either add that the variants being claimed need to have specific activities or to further define the term "TANGO-69 receptor activity" as detailed above. Applicant has additionally amended claims 30-32 and 34 to increase the percent identity of the variants being claimed, as detailed above. Finally, Applicant has cancelled claims 28-29 and 33 without prejudice.

Therefore, the polypeptides described in remaining claims 23, 24, 26, 27, 30-32 and 34-38 now only vary by either 5% or 2% from SEQ ID NO:19 or 18 and the polypeptides described in these claims must additionally have activities specific to TANGO-69 receptor molecules as defined in the specification. As described above in detail, the limitations within these amended claims are fully enabled within the specification as Applicant has provided teachings for every element needed for one of skill in the art to practice the claimed invention. Specifically, Applicant's disclosure provides teachings sufficient to enable one of skill in the art to identify regions of importance within the claimed polypeptide, to generate variants of the polypeptide and to assay the variants for the desired activities.

Therefore, contrary to the Examiner's assertions, Applicants have provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. Therefore, Applicant respectfully

requests reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph rejection over claims 23, 24, 26-38.

VII. Rejection of Claims 24, 25 and 31 Under 35 U.S.C. § 112, first paragraph

Claims 24, 25, and 31 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner notes that said claims "require access to the ATCC deposited plasmid recited in the claims," and that "[a]s a required element the plasmid must be [...] readily available to the public."

Applicant submits that the deposit referred to in claims 24, 25 and 31 and in new claim 41, has been accepted by ATCC, an international Depository Authority, under the provisions of the Budapest Treaty. As evidence of this deposit, Applicant submits herewith a copy of the ATCC receipt for this biological deposit (*E. coli* DH5α transformed with human T198b in the plasmid vector pMET7, Epthdc089g02, as ATCC designation number 207173), as well as a declaration that the deposit was made in accord with the terms of the Budapest Treaty.

Applicants therefore request withdrawal of the rejection with respect to claims 24, 25, and 31.

VIII. Rejection of Claims 30-34, 37 and 38 Under 35 U.S.C. § 102(e)

Claims 30-34, 37 and 38 are rejected under 35 U.S.C. §102(e), as being anticipated by Spear et al. (US 6,303,336). The Examiner states that "[S]pear teaches a polypeptide which is soluble and which comprises a sequence that is 92.5% identical to that of SEQ ID NO:18" in the present application. In an effort to expedite prosecution, and without in any way acquiescing to the Examiner's rejection, Applicant has amended a) claim 30 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 95% identical to the nucleic acid sequence of SEQ ID NO:19; and b) claim 31 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 98% identical to the nucleic acid sequence of SEQ ID NO:19. Amendment of claims 30 and 31 thereby obviates the foregoing 35 U.S.C. §102(e) rejection as a nucleic acid sequence that is at least 95% identical to SEQ ID NO:19 would necessarily encode a polypeptide of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:18.

Applicant has additionally amended i) claim 32 to read that the polypeptide comprise an amino acid sequence which is at least 95% identical to the amino acid sequence of SEQ ID NO:18; and ii) claim 34 to read that the polypeptide of claim 32 is at least 98% identical to the amino acid sequence of SEQ ID NO:18. Support for the claim amendments can be found in the specification, for example on page 15, line 24. Applicant therefore respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §102(e) rejection.

IX. Rejection of Claims 30-34, 37 and 38 Under 35 U.S.C. § 102(b)

Claims 30-34, 37 and 38 are rejected under 35 U.S.C. §102(b), as being anticipated by Montgomery et al. (Cell 1996). The Examiner states that "[M]ontgomery teaches the same fusion protein as Spear et al. 6,303,336, and further teaches that the fusion protein blocks herpesvirus infection". In an effort to expedite prosecution, and without in any way acquiescing to the Examiner's rejection, Applicant has amended a) claim 30 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 95% identical to the nucleic acid sequence of SEQ ID NO:19; and b) claim 31 to read that the polypeptide must be encoded by a nucleotide sequence which is at least 98% identical to the nucleic acid sequence of SEQ ID NO:19. Amendment of claims 30 and 31 thereby obviates the foregoing 35 U.S.C. §102(b) rejection as a nucleic acid sequence that is at least 95% identical to SEQ ID NO:19 would necessarily encode a polypeptide of at least 95% sequence identity to the amino acid sequence of SEQ ID NO:18. Applicant has additionally amended i) claim 32 to read that the polypeptide comprise an amino acid sequence which is at least 95% identical to the amino acid sequence of SEQ ID NO:18; and ii) claim 34 to read that the polypeptide of claim 32 is at least 98% identical to the amino acid sequence of SEQ ID NO:18. Support for the claim amendment can be found at least beginning on page 15, line 24. Applicant therefore respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §102(b) rejection.

CONCLUSION

In view of the amendments, claim cancellations and remarks made herein, Applicant respectfully submits that the rejections presented by the Examiner are now overcome and that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

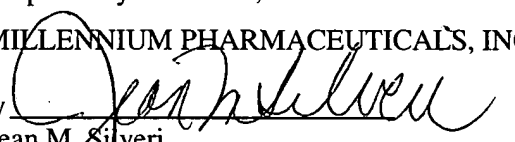
It is believed that this paper is being filed timely and that a three month extension of time is required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

November 14, 2003

MILLENNIUM PHARMACEUTICALS, INC.

By 

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